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EXAMINER	
LI, BAO Q	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 08/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/824,796	KADAN ET AL.	
	Examiner	Art Unit	
	Bao Qun Li	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-6,10-22,25 and 26* is/are pending in the application.

4a) Of the above claim(s) *3, 10-13 and 20-22, 25-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-6 and 14-19* is/are rejected.

7)☒ Claim(s) *5,14-17 and 19* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *07/14/2006* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

This is a response to the amendment filed on 05/22/06. Claims 1, 14 and 25 have been amended. Claims 2, 7-9, 23-24 have been canceled. Claims 1, 3-6, 10-22 and 25-26 are pending. Clams 3, 10-13, 20-22 and 25-26 are withdrawn from the consideration. Claims 1, 4-6, 14-19 in the scope of E1a and E2F are considered before the examiner.

Applicants are reminded that there was a typographic error in the response because applicants only cited that claims 1-2 stand rejected. Upon considering that applicants had addresses the whole issue of 103 rejection of all rejected claims, the response is not incomplete. However, the office requires an appropriate response to each of the outstanding rejections covering all the rejected claims raised in the current office action.

Please note any ground of rejection(s) that has not been repeated is removed.

Interview Summery

Regarding claim 5 and its dependent claims 14-15, a telephone interview was conducted with applicants' representative, attorney Linda R. Judge on July 14, 2006. She had clarified that the heterologous transcriptional regulatory element (TRE) cited in claim 5 is the heterologous TRE, i.e. E2F cited in claim, and said E2F is the first TRE cited in the dependent claims 14 and 15.

(Note: Although applicants' representative of attorney Linda Judge has clarified which the heterologous TRE cited in claim 5 and its dependent claims is referred to, an objection as well as a rejection over said claims still need to be made on the record until applicants officially amend the claims.

MPEM (2143.03): A claim limitation, which is considered indefinite, cannot be disregarded. If a claim is subject to more than one interpretation, at least one of which would render the claim unpatentable over the prior art, the examiner should reject the claim as indefinite under 35 U.S.C. 112, second paragraph (see MPEP § 706.03(d)) and should reject the claim over the prior art based on the interpretation of the claim that renders the prior art applicable).

Claim objection

1. Claim 5 is objected to under 37 CFR 1 .75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim 1. In the instant case, the failure to further limit the claim 1 is caused by the uncleanness of the claim 5 to define which the cited TRE in claim 5 is referred to. Applicants are required to cancel the objected claim, or amend the objected claims to place said claim in a proper dependent form, or rewrite the claim in an independent form. Claim 6 and 14-15 are also objected for the same reason since the TRE cited in claim 5 is not defined.

2. This new ground of objection is necessitated by applicants' amendment.

Claim Rejections - 35 USC § 112 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. The rejection of claim 4 under 112 2nd paragraph has been overcome by the amendment of claim 1.

4. Claim 5 is vague and indefinite in that it is unclear the structural characteristic of cited vector is not clearly defined. In the instant case, claim 5 is a dependent claim of claim, however, it fails to further limit the independent claim 1. It is unclear which heterologous TRE cited in the claim is referred to and how many TREs are constructed into the cited adenovirus vector. This rejection affects the dependent claims 14-17 and 19 set forth below:

5. The previous of 112 2nd paragraph rejection of claims 14-15 has been withdrawn in view of applicants' amendment. However, a new ground rejection on these claims 14-15 under 112 2nd paragraph has been re-established necessitated by applicants' amendment of claim 5. In the instant case, claims 14-15 depend on claim 5, however, claim 5 fails to define how many TREs are there in the cited adenovirus vector, and which TRE cited in claim 5 is referred to. Consequently, it is also unclear which TRE is the 1st TRE and which TRE is the 2nd TRF cited in claims 14 and 15. This rejection also affects claims 16-17.

Claim Rejections - 35 USC § 112 1st paragraph

6. The rejection of claims 1, 4-6, 14-19 under 35 U.S.C. 112, first paragraph has been withdrawn in view of applicants argument and state of art on the ground that CAR, $v\alpha_v\beta5$ integrins (veronectin) and CD46 are currently recognized as the receptors for different serotypes of adenoviruses binding and infection to a host cell, wherein Hela S3 cell are the host cell that expresses as all of these receptors (See Iacobelli-Martinez et al. J Virol. 2005 September; 79(17): 11259–11268, see 1st paragraph of Discussion on page 11264, Wu et al. J. Virol. 2004, Vol. 78, No. 8, pp. 3897-3905, see 3rd paragraph of the 2nd column in page 3900, Turturro et al. (Blood, 1998, Vol. 92, No. 10, Suppl. 1, part 1-2, pp. 381B, abstract #4640 and Technical Bulletin, published on 2006 by SAFE Bioscinces, Inc).

7. Moreover, regarding the trans-complement element requirement issue for the previous rejected claim 4, upon reconsidering the claimed invention, the rejection is also removed because the adenovirus vector cited in claim 4 is a replication-competent adenovirus vector, no trans-complement element needs to be provided by a host cell. In addition, the deletion of Rb binding site can be made in CR1 and/or CR2 domains without interrupting the replication essential region of CR3 in E1a.

Claim Rejections - 35 USC § 102

8. The rejections of claims 1-2 and 18 under 35 U.S.C. 102(b) have been withdrawn necessitated by the applicants' amendment.

Claim Rejections - 35 USC § 103

9. Claims 1, 5-6, 16-19 are still rejected under 35 U.S.C. 103(a) as being unpatentable over WO 02/067861A2 and Turturro et al. (Blood, 1998, Vol. 92, No. 10, Suppl. 1, part 1-2, pp. 381B, abstract #4640) under the same ground stated in the previous office action. The argument has been moot in the view of the new ground rejection. A response and the new ground of the modified 103 rejection of claims 1, 5-6, 14-15 and 16-19 are addressed in detail set forth below:

10. Claims 1, 5-6, 14-15 and 16-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 02/067861A2 and Turturro et al (Blood, 1998, Vol. 92, No. 10, Suppl. 1, part 1-2, pp. 381B, abstract #4640), which is substantiated by the detail disclosure of Turturro et al. (b)

(Clinical Cancer Research 2000, Vol. 6, pp. 185-192). This is a new ground of rejection that is necessitated by applicants' amendment of claims 1 and 14.

(Note: The ground of the rejection is based on the interpretation of the TRE cited in claim 5 is the heterologous TRE, i.e. E2F of claim 1, and the E2F is the first TRE implicated in the dependent claims 14-17 on the record).

11. After amendment, the claimed invention is directed to a Hela S3 cell or a Hela S2 cell line comprising a tumor or tissue specific recombinant replication-competent adenovirus, wherein said adenovirus vector comprises a heterlogous E2F-responstive transcriptional regulatory element (TRE), operatively linked to an E1a coding region (Claims 1, 18), wherein said adenovirus vector further comprises a heterologous therapeutic gene encoding a polypeptide of GM-CSF. Another embodiment of these rejected claims is also directed to a host HelaS3 cell comprising a replication-competent adenovirus virus that further comprises a second different heterologous TRE operatively linked to a second adenovirus essential gene that control the replication of said adenovirus vector.

12. In the response, applicants admit that the reference of WO 02/067861A2 teaches a recombinant adenovirus vector comprising an adenovirus 5 or 35 backbone wherein the virus vector comprises a left ITR, a terminal signal sequence, an E2F responsive prompter operatively linked to an E1a gene, an adenoviral packaging signal and a right ITR, and the reference by Turturro et al. teach Hela S3 cells expressing high levels of CAR, which make them susceptible to infection by adenovirus.

13. However, Applicants still submit that WO 02/067861A2 does not teach to use Hela S3 cells for propagating said adenovirus vector. The references provide no motivation to combine the references, and absence of hindsight, afforded by the absence of the present invention as roadmap, one skill in the art relying on WO 02/067861A2 would not look to every reference for culturing adenovirus and settle on Turturro et al.

14. Applicants' argument has been respectfully considered; however, it is not found persuasive to withdrawn the rejection because is a 103 obvious rejection is made with more than one cited references, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413,

208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

15. Moreover, regarding the argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that the judgment on obviousness of current application is not in a sense necessarily a reconstruction based upon hindsight reasoning, But it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

16. Regarding Sources of Rationale Supporting a Rejection Under 35 U.S.C. 103, MPEP 2144 cites: RATIONALE MAY BE IN A REFERENCE, OR REASONED FROM COMMON KNOWLEDGE IN THE ART, SCIENTIFIC PRINCIPLES, ART- RECOGNIZED EQUIVALENTS, OR LEGAL PRECEDENT. In particular, MPEP points out that "The rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). See also In re Kotzab, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000) (setting forth test for implicit teachings); In re Eli Lilly & Co., 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990) (discussion of reliance on legal precedent); In re Nilssen, 851 F.2d 1401, 1403, 7 USPQ2d 1500, 1502 (Fed. Cir. 1988) (references do not have to explicitly suggest combining teachings); Ex parte Clapp, 227 USPQ 972 (Bd. Pat. App. & Inter. 1985) (examiner must present convincing line of reasoning supporting rejection); and Ex parte Levengood, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993) (reliance on logic and sound scientific reasoning).

17. MPEP also cites: THE EXPECTATION OF SOME ADVANTAGE IS THE STRONGEST RATIONALE FOR COMBINING REFERENCE. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that

some advantage or expected beneficial result would have been produced by their combination. In re Sernaker, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983).

18. In the instant case, claims 1, 5-6 and 14-19 considered as a whole is directed to a Hela S3 cell or Hela S3 cell line comprising a tissue or tumor specific recombinant replication-competent adenovirus vector as described above. Therefore, the patentability of the claims comprises two important elements, one is the Hela S3 cell and another is a unique adenovirus vector, and it can be determined either by the novelty of the HeLa S3 (if it comprise any unique feature not taught or disclosed by the cited prior art) or the claimed adenovirus vector (if it comprises any patentable distinct structural/functional feature(s)not taught or suggested by the cited prior art).

19. However, regarding the claimed adenovirus vector, the reference WO 02/067861A2 still teaches each and every limitation of the adenovirus vector cited in the rejected claims even after amendment. For example, WO 02/06861A2 teaches that "the present invention to provide novel oncolytic adenoviral vectors for the treatment of neoplastic disease, which exhibit a high degree of tumor selectivity, therapeutic efficacy, and safety when administered to a host organism (see last paragraph of page 1). In a particularly preferred embodiment, the oncolytic adenoviral vector has an E2F promoter operably linked to the Ela gene and the human telomerase reverse transcriptase promoter operably linked to the E4 gene (the 2nd paragraph of page 14). In particular, the gene(s) essential for the replication of said oncolytic adenoviral vectors is controlled by E2F-responsive promoters, wherein the E2F is selectively transactivated in cancer cells (the 4th paragraph of page 15). WO 02/06861A2 also teaches that preferably, the E2F-responsive promoter is a mammalian E2F promoter; more preferred is a human E2F promoter (the 2nd paragraph of page 19 and claims 1-5 and Fig. 6 & 48). WO 02/06861A2 also teaches that in a preferred embodiment of the invention, said adenoviral vector carries at least one therapeutic transgene, preferably, a cytokine such as GM-CSF that can stimulate a systemic immune response against tumor (the last paragraph of page 14, and claims 8, 14-16, 18-23). WO 02/06861A2 also teaches that the DNA sequence encoding said therapeutic gene is under the control of a suitable promoter, wherein a suitable promoter includes, but are not limited to, adenoviral promoters, such as the adenoviral major late promoter and/or the E3 promoter', or hetorologous promoters, such as the cytomegalovirus (CMV promoter; the Rouse Sarcoma Virus (RSV) promoter; inducible promoters, such as the MMT promoter, the metallothionein promoter;

heat shock promoters; the albumin promoter and the Apo Al promoter. In a preferred embodiment, the promoter is a tissue-specific promoter. An E2F-responsive promoter is particularly preferred, such as the human E2F-1 promoter (See the 1st paragraph of 25). The tumor specific adenovirus vector taught by WO 02/06861A2 is also a recombinant replication-competent adenovirus vector because WO 02/06861A2 teaches that said oncolytic adenovirus vector does not loss any essential region that control said adenovirus replication, and WO 02/06861A2 points out that the oncolytic adenovirus vectors constructed by their novel designs are able to replicate in any cell line or tumor cells that do not contain any trans complement gene(s) (Please see last paragraph of 92 through 94, Table 31 on page 102, example 16 on pages 101-102, page 107-110, example 21 in pages 142-143). WO 02/067861A2 also teaches that the said adenovirus vector may further comprise another tissue specific promoter operably linked to another adenovirus essential region E4 (See claims 9-13). Therefore, the adenovirus vector(s) taught by WO 02/067861A2 meet each and every limitation of the claimed adenoviruses vector(s).

20. Regarding Hela S3 cell, the reference of Turturro et al. teaches that Hela S3 is a regular positive host cell used for the adenovirus or adenovirus vector transduction or infection, wherein said Hela S3 cell expresses significant highest levels of the adenovirus receptors CAR and $\alpha_v\beta$ integrins compared with other test cell lines (For more detail date, please see Turturro et al. (b), Fig. 4 on page 190). It is worth to note that the claimed Hela S3 cell is the same Hela S3 cell taught by Turturro et al. that applicants does not make any genetic change about the cell itself nor find any new receptor(s) affiliated or assistant to the claimed adenovirus binding or infection except the claimed Hela S3 cell comprising a tissue or tumor specific replication-competent adenovirus vector. However, said adenovirus vector is the same adenovirus vector taught by WO 02/067861A2.

21. It is well known in the art that Hela S3 cell has lone been recognized accepted as a positive susceptible host cell or host cell line for generating or propagating wild-type adenovirus or replication competent adenovirus vector. This fact has been evidenced and reinforced by the disclosure of Turturro et al. More Importantly, Turturro et al. provides solid scientific basis about why Hela S3 should be chosen by an ordinary skilled in the art for preparing adenoviruses vector in gene therapy because the Hela S3 cell expresses highest levels of the adenovirus

receptors CAR and $\alpha_v\beta5$ compared with other test cell lines (For detail data, please see Turturro et al. (b) Fig. 4 on page 190). For example, regarding why they need to test the adenovirus receptors CAR and $\alpha v\beta$ integritins expression prior to selection of a host cell for the adenovirus mediated gene transfer and therapy, Turturro et al. conclude at the end of their investigation that a presence of a significant expressions of CAR and of the $\alpha_v\beta5$ integrins on a cell line may predict the potential efficiency of such approach (See entire abstract, especially the last sentence of the paragraph). This conclusion apparently teaches and suggests that any cell expressing high levels of adenovirus receptors should be used as an efficiency adenovirus transducing host cell line for preparing the adenovirus mediated gene therapy vector. Hela S3 cell should be certainly selected as the best positive susceptible host cell line in the art because it expresses the highest levels of adenovirus binding receptors.

22. Therefore, it would have been obviously for any ordinary skilled in the art to be motivated for using the Hela S3 cell for producing said replication-competent recombinant adenovirus vector taught by WO 02/067861A2 absence of unexpected result. Because the reference of WO 02/067861A2 teaches how to make the claimed tissue or tumor specific recombinant replication-competent adenovirus and the prior art has approved and used Hela S3 cell as a positive adenovirus or replication-competent adenovirus vector transducing and infection as evidenced by Turturro et al. More importantly, Turturro et al. also has approved that Hela S3 cell is the most susceptible host cell for generating or propagating a replication-competent adenovirus vector since it expresses highest level of adenovirus receptors CAR and $\alpha v\beta5$.

23. The rationale to modify or combine the cited prior art in that instant case, does not have to be expressly stated in the prior art; the rationale is expressly or impliedly contained in the cited prior art or it can be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles. In the current case, an ordinary skilled in the art, who does not need to read the current application as road map to find Hela S3 as the best host cell, because prior the current application was filed, the art has lone been accepted and used Hela S3 cell as a positive cell for the adenovirus transducing and infection. The claimed adenovirus vector has also been taught by the cited prior art prior to the application was filed.

24. Regarding applicants' comment that other adenovirus use CD46 as receptor, Applicants are reminded that CD46 is a receptor expressed by any nuclear cell. Hela S3 cell as a nuclear cell also expresses said receptor.

25. To this context, since there is no unexpected result being provided, the claimed invention as a whole is still considered as prima facie obvious absence unexpected results. The rejection is maintained.

Claim Rejections - 35 USC § 103

26. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

27. Claims 1, 4-6 and 14-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johnson et al. (a) (Patent No. 7,001,596B1) or Johnson et al. (b) (Cancer Cell May 2002, Vol. 1, pp. 325-327) in view of Turturro et al. (Blood, 1998, Vol. 92, No. 10, Suppl. 1, part 1-2, pp. 381B, abstract #4640), which is substantiated by the detail disclosure of Turturro et al. (b) (Clinical Cancer Research 2000, Vol. 6, pp. 185-192). This is a new ground rejection necessitated by applicants' amendment.

28. The claimed invention is directed to Hela S3 cell or Hela S2 cell line comprising a tumor or tissue specific recombinant replication-competent adenovirus, wherein said adenovirus comprises a heterlogous E2F-responstive transcriptional regulatory element (TRE), operatively linked to an E1a coding region (Claims 1, 18). Another embodiment of the claimed invention in claims 5-6, 14-17 and 19 is directed to a Hela S3 cell or Hela cell line further comprising second heterologous TRE in addition to the first heterologous E2F, operatively linked to a second adenovirus essential region. The second kind of adenovirus vector also comprises a heterologous gene encoding GM-CSF. Another embodiment of the claimed invention (claim 4) is also directed to a Hela cell comprising a tumor or tissue specific recombinant replication-competent

adenovirus, wherein said adenovirus comprises a heterlogous E2F-responstive transcriptional element (TRE), operatively linked to an E1a coding region, wherein said E1a gene is mutated to encode a protein lacking the capacity to bind to RB.

29. The vector also comprises a heterologous gene encoding GM-CSF. Another embodiment of the claimed invention (claim 4) is also directed to a Hela S3 cell comprising a tumor or tissue specific recombinant replication-competent adenovirus, wherein said adenovirus vector comprises a heterlogous E2F-responstive transcriptional element (TRE), operatively linked to an E1a coding region, wherein said E1a gene is mutated to encode a protein lacking the capacity to bind to RB.

30. Both references by Johnson et al. (a) or Johnson et al. (b) teach a tumor or tissue-specific replication-competent adenovirus vector, and method for making the same, wherein said replication competent adenovirus vector can substantially and selectively kill neoplastic cells with little or no killing on non-nepoplastic cells because said adenovirus vector comprises at least one, and preferably two tumor cell specific transcriptional unit, a heterologous gene regulatory element, such as at least one human E2F that substitutes the basic adenovirus E1a promoter, including CAAT box and TATA box and also operably links to the E1a coding region. The preferable promoters regions that are substituted with said human E2F are E1a and/or E4 promoter regions. Moreover, the E1a gene also comprises a further mutation(s) in CR1 and/or the CR2 domains that are responsible for binding to the RB protein (See lines 58-67 in column 4, lines 1-40 in column 5, lines 5-10 in column 6, lines 42-49 in column 7, lines 30-37, lines 54-67 in column 12, lines 19-30 in column 13 and lines 1-30 in column 15 for (a), claims 1-11 and Fig. 1 in page 327 of (b)). Johnson et al. (a) and (b) explicitly teach a method about how to mutate the Rb binding sites in RC1 and/or RC2 domain (See column 3 for (a) and pages 326-327 for (b)) without interrupting the essential region in CR3 that control said adenovirus replication. Johnson et al. (a) also teach that said adenovirus vector contains heterologous therapeutic gene, such as GM-CSF inserted in the E1a and /or E4, or preferably E1b, or E3 regions (See lines 15-41 in column 17). In addition, Johnson et al. (a) teach several suitable or desirable higher eukaryotic cell lines for propagating the said replication competent adenovirus vector, which include Hela cells (See lines 50-65 in column 10). Johnson et al. (a) do not explicitly teach that the Hela cell is the Hela S3 cell. However, it is well know that Hela S3 cell is the homogeneous culture of a

cloned single Hela cell, which does not have any other genetic engineered manipulation compared with the parental one except for more homogeneous cell population.

31. Regarding Hela S3 cell, the reference of Turturro et al. teaches that Hela S3 is a regular positive host cell used for the adenovirus or adenovirus vector transduction or infection, wherein said Hela S3 cell expresses significant highest levels of the adenovirus receptors CAR and $\alpha_v\beta$ integrins compared with other test cell lines (For more detail date, please see Turturro et al. (b), Fig. 4 on page 190). It is worth to note that the claimed Hela S3 cell is the same Hela S3 cell taught by Turturro et al. that applicants does not make any genetic change about the cell itself nor find any new receptor(s) affiliated or assistant to the claimed adenovirus binding or infection except the claimed Hela S3 cell comprising a tissue or tumor specific replication-competent adenovirus vector. However, said adenovirus vector is the same adenovirus vector taught by the cited prior art of Johnson et al. (a) (Patent No. 7,001,596B1) or Johnson et al. (b) (Cancer Cell May 2002, Vol. 1, pp. 325-327).

32. It is well known in the art that Hela S3 cell has lone been recognized accepted as a positive susceptible host cell or host cell line for generating or propagating wild-type adenovirus or replication competent adenovirus vector. This fact has been evidenced and reinforced by the disclosure of Turturro et al. More Importantly, Turturro et al. provides solid scientific basis about why Hela S3 should be chosen by an ordinary skilled in the art for preparing adenoviruses vector in gene therapy because the Hela S3 cell expresses highest levels of the adenovirus receptors CAR and $\alpha_v\beta5$ compared with other test cell lines (For detail data, please see Turturro et al. (b) Fig. 4 on page 190). For example, regarding why they need to test the adenovirus receptors CAR and $\alpha v\beta$ integritins expression prior to selection of a host cell for the adenovirus mediated gene transfer and therapy, Turturro et al. conclude at the end of their investigation that a presence of a significant expressions of CAR and of the $\alpha_v\beta5$ integrins on a cell line may predict the potential efficiency of such approach (See entire abstract, especially the last sentence of the paragraph). This conclusion apparently teaches and suggests that any cell expressing high levels of adenovirus receptors should be used as an efficiency adenovirus transducing host cell line for preparing the adenovirus mediated gene therapy vector. Hela S3 cell should be certainly

selected as the best positive susceptible host cell line in the art because it expresses the highest levels of adenovirus binding receptors.

33. Therefore, it would have been obviously for any ordinary skilled in the art to be motivated for using the Hela S3 cell for producing said replication-competent recombinant adenovirus vector taught by (Patent No. 7,001,596B1) or Johnson et al. (b) (Cancer Cell May 2002, Vol. 1, pp. 325-327 absence of unexpected result. Because the reference of (Patent No. 7,001,596B1) or Johnson et al. (b) (Cancer Cell May 2002, Vol. 1, pp. 325-327) teaches how to make the claimed tissue or tumor specific recombinant replication-competent adenovirus and the prior art of Turturro et al. (a) has provided the evidence about why Hela S3 cell should be used as the most susceptible host cell for generating or propagating a replication-competent adenovirus.

34. MPEP cites: THE EXPECTATION OF SOME ADVANTAGE IS THE STRONGEST RATIONALE FOR COMBINING REFERENCE. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Sernaker, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983).

35. In the current case, an ordinary skilled in the art, who does not need to read the current application as road map to find Hela S3 as the best host cell, because prior to the current application was filed, the art has lone been accepted and used Hela S3 cell as a positive cell for the adenovirus transducing and infection as evidenced by the cited reference of Turturro et al. (a) . The claimed adenovirus vector has also been taught by the cited prior art of (Patent No. 7,001,596B1) or Johnson et al. (b) (Cancer Cell May 2002, Vol. 1, pp. 325-327) prior to the application was filed.

36. Hence, the claimed invention as a whole is prima facie obvious absence of unexpected results.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bao Qun Li, MD. whose telephone number is 571-272-0904. The examiner can normally be reached on 6:30 am to 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Baoqun Li

Bao Qun Li

BAOQUN LI, MD
PATENT EXAMINER

Aug. 04/2006